2/2/82

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

001453

MEMORANDUM

DATE:

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: EPA Reg. No. 464-546. Submission of Additional Data to Support Registration of Garlon 3A Herbicide.

TOX Chem. No: 882I

FROM: D. G. Van Ormer DVO
Toxicology Branch/HED (TS-769)

TO: PM Team No. 25
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch/HED (TS-769) 2/2/82

Action Requested:

Toxicology Branch (memo E. R. Budd, April 2, 1979) has asked applicant to submit a second teratogenicity study (preferably in rabbits) prior to full registration of Garlon 3A Herbicide. The teratogenicity study reviewed in that memo showed that in rats at the high dose (200 mg/kg/day) 2/277 fetuses showed multiple major anomalies. An additional acute oral study was also requested to be performed in rats, male and female. Mutagenicity data were reviewed by I. Mauer and W. R. Schneider.

Conclusions:

The teratogenicity study on Garlon in rabbits reviewed below constitutes minimum data to support the lack of teratogenicity of Garlon. The study fails to show a no-effect level for fetotoxicity ("observable adverse effects attributable to the test substance": minor anomalies and increased normal variants). The appearance of major terata was not significantly different from the incidence reported in concurrent controls.

The acute oral studies in rats (male and female) and in mice (male) fulfill agency requirements for the tests as reported.

1. Teratogenicity Study of Triclopyr (Technical)

Effect of Dowco® 233 on Pregnancy of the New Zealand White Rabbit. Accession No. 242367. Performed by Huntingdon Research Centre for Dow Chemical Company.

A. Procedure:

Dowco® 233 (Sample No. AGR 134832) was administered to New Zealand White rabbits (2.8-3.8 kg) by intubation (1 ml/kg) in corn oil on days 6 thru 18 of pregnancy, at dosages of 0, 10, and 25 mg/kg/day. Each dosage group consisted of 20 rabbits. Does were maintained in individual cages under controlled temperature, relative humidity, and light. Diet and tap water were ad libitum. Daily observation was accompanied by weighing on days 1, 6, 10, 14, 19, 23, and 29 of pregnancy.

On day 29 of pregnancy, the animals were killed by cervical dislocation, and the ovaries and uteri were examined immediately to determine values for parameters as follows: number of corpora lutea, number and distribution of live young, number and distribution of embryonic/fetal deaths, individual fetal weight, and fetal abnormalities.

Live young were examined externally, weighed, dissected, examined internally, and sexed. Fixing was performed with 74 OP industrial methylated spirit. Brains were examined prior to clearing and staining (by the modified Dawson technique) for skeletal examination.

B. Results:

Interpretation of maternal toxicity was somewhat clouded by a high rate of enteric disorder in dams, particularly in the control (3/20) and high-dose (6/20) groups. A possible direct or indirect influence of treatment with Dowco® 233 at 25 mg/kg cannot be excluded as a contributory factor to mortality. Maternal toxicity, considered as decrease in weight gain (Figure 1 of the Report), was treatment related only during the last third of the treatment period, and not markedly dose-dependent. Maternal weight change was selectively summarized for unexplained reasons. Terminal autopsy of dams revealed mainly indications of enteric disorder.

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Litter data showed no significant intergroup differences in pregnancy rate, live young, embryonic deaths, implantations, corpora lutea, total implantation loss, and litter weight. Major malformations were reported as occurring in 1.3% (1/81) control fetuses (rhinencephaly with fusions of orbital sockets and other areas, encephalocele with underdeveloped maxillae); in 1.3% (2/132) of the low-dose fetuses (sternebral abnormalities, cebocephaly with fused facial and maxillary areas, internal hydrocephaly); and in 1.4% (1/108) of the high-dose fetuses (bilateral microphthalmia with folding and dysplasia of the retina and hemorrhage into the retinal chamber). The low-dosage group exhibited (Table 4 of the Report) a 2.7-fold increase over controls in "minor skeletal anomalies" (asymmetrical sternebrae, etc.). The high-dose group showed a 2-fold increase in minor skeletal anomalies. Extra ribs developed in 48% and 42% of the fetuses at low- and high-dose levels, respectively, vs. 37% for controls. (Affected progeny of two dams were excluded from the summary table, Table 5, for unexplained reasons). Unossified sternebrae also showed an increased incidence: 23% at low dose and 25% at high dose vs. 13% for controls.

C. Core-Classification: Minimum Data:

1. Study employed only two treatment levels, not spaced logarithmically.

2. Maternal mortality at the high-dose level was greater than 10% (viz., 30%). Most of these deaths were attributed to enteritis, which could not be excluded as treatment-related. Maternal toxicity presented as bodyweight change (Figure 1 of the Report) was only marginally demonstrated and only weakly dose dependent.

3. The low-dosage group was not devoid of observable toxicity.

4. Crown-rump measurements were not reported.

5. Group means are not accompanied by measures of variability, although historical control data is presented.

2. Rat Acute Oral Toxicity of Triclopyr (Technical)

Toxicology Research Laboratory, Dow Chemical, U.S.A., Midland, Michigan. April 28, 1980. Accession No. 242367.

A. Procedure:

The test material was Sample No. AGR 134832 of Triclopyr, also known as DOWCO® 233 pesticide or (3,5,6-trichloro-2-pyridyloxy) acetic acid, a white solid.

Five dosage groups of rats (Sprague-Dawley, spartan; 178-331 g) consisting of 6 rats/sex/dose level, were acclimatized a week and then fasted overnight prior to dosing. Administration of test material was by single-dose gavage as a 10% solution in acetone/corn oil (1:9) at dosages of 200, 400, 630, 800, or 1600 mg/kg. Animals were housed 2 or 3 per cage under controlled lighting and with feed and water ad libitum. The two-week post-dosing observation period included periodic observation and 3 weighings. Survivors were submitted for gross pathological examination. The median lethal dose was calculated by the moving average method (Thompson and Weil, 1952). The slope was calculated as log (LD84/LD16).

B. Results:

All surviving rats gained weight. Rats of both sexes in the three upper-dose groups showed diarrhea, piloerection, and lethargy. Females of the low two doses also were lethargic. Some females at the upper three doses exhibited dark exudate around the nose.

One male of the 800 mg/kg group showed a moderately decreased thymus; this effect in stated as possibly stress related, as evidenced by marked decrease in weight gain.

All other lesions observed at gross necropsy were stated to be either spontaneous or not treatment related. Numerous animals showed focal petechial hemorrhage of the thymus.

Acute oral LD50, rats:

Males - 729 mg/kg
(95% conf. int. 515-1127; slope 6.92)

Females - 630 mg/kg
(95% conf. int. 450-829; slope 5.23)

Toxicity Category III.

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C. Classification: Core-Minimum Data.

1. Dosing volume not constant.

2. Not housed individually.

3. Not weighed daily.

4. List of organs examined not provided.

3. Mouse Acute Oral Toxicity of Triclopyr (technical). Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, Michigan. February 28, 1980. Accession No. 241930.

A. Procedure:

The test material was triclopyr, also known as DOWCO® 233 herbicide or (3,5,6-trichloro-2-pyridyloxy) acetic acid, a white solid.

Five male mice per dose level (COBS® CFR 1, Charles River; 28-43g) received doses of 126, 252, 500, 1000, or 2000 mg/kg of test material as a 10% suspension in acetone/corn oil (1:9) by single-dose gavage. The mice were fasted 16-18 hours prior to dosing. During the two-week observation period the mice were housed individually under controlled temperature, humidity, and light-cycle, with chow and water ad libitum. Periodic observation and three weighings were performed. Survivors were submitted for gross pathological examination. The acute oral median lethal dose was calculated by the method of Finney (1972).

B. Results:

Toxic signs involved lethargy, piloerection, and diarrhea. Treatment-related lesions were stated as darkened liver occurring in one mouse of the 252 mg/kg group and in one of two survivors at the 500 mg/kg group. The other surivivor of the latter group showed multiple minute pale foci along the borders of all lobes of the liver, consistent with focal necrosis. Corneal cloudiness was reported for several survivors.

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Acute oral LD50, male mice:
471 mg/kg
95% conf. int. 245-909; slope of probit line 1.95 (95% conf. int. 0.84-13.05).

Toxicity Category: II

C. Classification: Core-Minimum Data

1. Dosing volume not constant.
2. Animals not weighed daily.
3. Organs examined not explicity listed.

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